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# **Final efficacy and updated safety results of the randomized phase III BEATRICE trial evaluating adjuvant bevacizumab-containing therapy in triple-negative early breast cancer**

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**Purpose:** To assess the long-term impact of adding bevacizumab to adjuvant chemotherapy for early triple-negative breast cancer (TNBC).

**Methods:** Patients eligible for the open-label randomized phase III BEATRICE trial had centrally confirmed triple-negative operable primary invasive breast cancer (pT1a–pT3). Investigators selected anthracycline- and/or taxane-based chemotherapy for each patient. After definitive surgery, patients were randomized 1:1 to receive  $\geq 4$  cycles of chemotherapy alone or with 1 year of bevacizumab (5 mg/kg/week equivalent). Stratification factors were nodal status, selected chemotherapy, hormone receptor status, and type of surgery. The primary end point was invasive disease-free survival (IDFS; previously reported). Secondary outcome measures included overall survival (OS) and safety.

**Results:** After 56 months' median follow-up, 293 of 2591 randomized patients had died. There was no statistically significant difference in OS between treatment arms in either the total population (hazard ratio 0.93, 95% confidence interval [CI] 0.74–1.17;  $P = 0.52$ ) or pre-specified subgroups. The 5-year OS rate was 88% (95% CI 86–90%) in both treatment arms. Updated IDFS results were consistent with the primary IDFS analysis. Five-year IDFS rates were 77% (95% CI 75–79%) with chemotherapy alone versus 80% (95% CI 77–82%) with bevacizumab. From 18 months after first study dose to study end, new grade  $\geq 3$  adverse events occurred in 4.6% and 4.5% of patients in the two arms, respectively.

**Conclusion:** Final OS results showed no significant benefit from bevacizumab therapy for early TNBC. Late-onset toxicities were rare in both groups. Five-year OS and IDFS rates suggest that the prognosis for patients with TNBC is better than previously thought.

**ClinicalTrials.gov:** NCT00528567

**Key words:** breast cancer, triple negative, chemotherapy, bevacizumab, survival

**Key Message:** Final overall survival results of the open-label randomized phase III BEATRICE trial showed no significant benefit from the addition of 1 year of bevacizumab therapy to standard adjuvant chemotherapy for triple-negative breast cancer. These results are consistent with the previously reported analyses of the primary endpoint (invasive disease-free survival).

## **introduction**

In HER2-negative breast cancer, combining bevacizumab with chemotherapy significantly improves progression-free survival (PFS) in the metastatic setting [1–6] and the pathologic complete response (pCR) rate in the neoadjuvant setting [7–11]. However, accumulating phase III data in the adjuvant setting in both colon and breast cancers have shown no benefit from adding 1 year of bevacizumab therapy to standard chemotherapy [12–17]. Similarly, recently published data for another anti-angiogenic approach – vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibition – showed no benefit as adjuvant therapy for high-risk renal cell carcinoma [18]. Primary efficacy results from the BEATRICE trial in early triple-negative breast cancer (TNBC) showed no significant difference in invasive disease-free survival (IDFS; primary outcome measure) between adjuvant bevacizumab and non-bevacizumab regimens after first events in 393 (15%) of the 2591 randomized patients [15]. The stratified hazard ratio (HR) for IDFS was 0.87 (95% confidence interval [CI] 0.72–1.07;  $P = 0.18$ ). Interim overall survival (OS) results at the time of the primary analysis were immature, with events in 107 patients (8%) in the chemotherapy-alone group and 93 patients (7%) in the bevacizumab-containing group. Here we report extended follow-up data from the pre-specified OS analysis of BEATRICE at 56 months' median follow-up.

## **patients and methods**

### **study design**

BEATRICE was an open-label international randomized phase III trial. As described previously [15], eligible patients had operable primary invasive breast cancer (T1b–

T3 or T1a with ipsilateral axillary node involvement) centrally confirmed as HER2-negative and with hormone receptor status that was either negative (total Allred score of 0 or 2) or low (total Allred score of 3 [intensity score 1, proportion score 2]). Definitive surgery (breast conserving or mastectomy) had to be completed 4–11 weeks before randomization. Patients were aged  $\geq 18$  years with an Eastern Cooperative Oncology Group performance status of 0 or 1 and a left ventricular ejection fraction of  $\geq 55\%$  measured up to 3 months before randomization.

Before randomization, investigators selected chemotherapy for each patient from a pre-specified suite of standard chemotherapy regimens. After surgical resection, eligible patients were stratified by axillary nodal status (0 versus 1–3 versus  $\geq 4$  positive lymph nodes), selected chemotherapy (anthracycline versus taxane versus anthracycline and taxane), hormone receptor status (negative versus low), and type of surgery (breast conserving versus mastectomy). Patients were randomized to receive either chemotherapy followed by observation or the same chemotherapy combined with bevacizumab and followed by single-agent bevacizumab. Patients who underwent breast-conserving surgery received loco-regional adjuvant radiotherapy according to local guidelines. Bevacizumab was given at a dose equivalent to 5 mg/kg every week (15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks) with the selected chemotherapy. After completing chemotherapy, patients underwent clinical and laboratory assessments every 3 weeks for the first year after randomization. Thereafter, all patients had annual mammography and clinical review every 3 months for 2 years, then every 6 months for 2 years, and subsequently annual clinic visits coinciding with mammography. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) and recorded at every clinic visit. Safety reporting in the post-

treatment period (from 18 months after the first dose of study drug until end of study) was limited to newly occurring grade  $\geq 3$  adverse events, serious adverse events, and adverse events of special interest.

All patients provided written informed consent. The study was approved by the institutional review board at each participating center and was conducted according to the principles of Good Clinical Practice, the provisions of the Declaration of Helsinki, and other applicable local regulations.

### **statistical analysis**

The primary objective was to compare IDFS in patients treated with chemotherapy alone versus chemotherapy plus bevacizumab. The sample size was calculated based on assumptions relating to the primary outcome measure (IDFS), as described previously [15].

Secondary end points included OS, breast cancer-free interval, disease-free survival (DFS), distant DFS, and safety. The interim OS analysis and additional secondary end points were reported with the primary end point. The final OS analysis was planned to be performed after a median follow-up of approximately 5 years or after 340 deaths, whichever occurred first. A total of 340 deaths would provide 75% power to detect an OS HR of 0.75 with a two-sided log-rank test at 5% alpha.

Efficacy end points were tested using a two-sided stratified log-rank test. Kaplan-Meier estimates were plotted by treatment group. Treatment effects were estimated by HRs with 95% CIs based on Cox regression models. Unstratified and stratified analyses (applying the stratification factors used at randomization) were performed. Subgroups of interest were pre-specified in the statistical analysis plan and included



the stratification factors as well as other disease- and patient-related prognostic factors. SAS (version 8.2; SAS Institute Inc., Cary, NC) was used for all statistical analyses.

## **results**

### **patient population**

Between December 3, 2007, and March 8, 2010, 2591 patients were randomized; of these, 2559 received treatment (Supplementary Figure S1). Baseline characteristics and investigator-selected adjuvant chemotherapy regimens are summarized in Supplementary Table S1.

### **efficacy**

At the time of data cutoff for the final OS analysis (June 30, 2014), the median duration of follow-up from randomization was 56 months in both treatment groups. All patients had discontinued or completed study therapy. Overall, 293 patients had died (86% of the 340 estimated OS events for the final analysis). Most deaths were from breast cancer recurrence (131 of 147 [89%] deaths in patients treated with chemotherapy alone, 136 of 144 [94%] deaths in bevacizumab-treated patients, and one of two deaths in patients who received no study therapy). Causes of death in the remaining patients are summarized in Supplementary Table S2.

There was no statistically significant difference in OS between the two treatment groups either in the intent-to-treat population (stratified HR = 0.93, 95% CI 0.74–1.17; log-rank  $P$  = 0.52; Figure 1) or in any of the pre-specified subgroups (Figure 2).

The unstratified analysis of OS showed similar results (unstratified HR = 0.94, 95% CI 0.75–1.18; log-rank  $P$  = 0.61).

Results of an exploratory analysis updating IDFS at the time of this final OS analysis were very consistent with those of the primary analysis (Supplementary Figure S2). The stratified HR was 0.87 (95% CI 0.73–1.03). The 5-year IDFS rates in this updated exploratory analysis were 76.9% (95% CI 74.4–79.4%) with chemotherapy alone and 79.6% (95% CI 77.2–81.9%) with bevacizumab-containing therapy.

At the time of data cutoff, bevacizumab therapy had been recorded after an IDFS event in 34 patients (2.6%) in the chemotherapy-alone arm and 13 patients (1.0%) in the bevacizumab-containing arm (12.6% versus 5.3%, respectively, of those with IDFS events).

## **safety**

In the post-treatment safety reporting period there were relatively few grade  $\geq 3$  adverse events in either arm (4.6% and 4.5% in the chemotherapy-alone and bevacizumab-containing arms, respectively) and no relevant differences between treatment arms were observed (Table 1). The only grade  $\geq 3$  adverse events occurring in more than two patients in either treatment group were hypertension and deep vein thrombosis, which occurred in 0.3% and 0.2% of patients, respectively, in the chemotherapy-alone group but were absent in the bevacizumab-containing group. The incidences of adverse events of special interest occurring from 18 months after the first dose of study drug until the end of the study were very similar between the two treatment arms (Supplementary Table S3). Detailed cardiac safety analyses based on the final data cutoff described here will be reported separately.

## discussion

The final OS analysis of the BEATRICE trial after 293 deaths showed no statistically significant benefit from adding bevacizumab to standard adjuvant chemotherapy for patients with early TNBC. Results of exploratory updated analyses of IDFS were similar to those from the primary IDFS analysis, showing no difference between the treatment arms (Supplementary Table S4). No new safety signals were identified with long-term follow-up and the safety profile was consistent with the established safety profile of bevacizumab in metastatic breast cancer [19] and the primary analysis of the BEATRICE trial [15].

Since the publication of the primary results from BEATRICE, two additional phase III trials evaluating bevacizumab as adjuvant therapy for early breast cancer have been reported: the BETH trial ( $N = 3509$ ) in HER2-positive disease [16] and the E5103 trial ( $N = 4994$ ) in lymph node-positive or high-risk node-negative HER2-negative disease [17]. None of these three randomized phase III trials (BEATRICE, BETH, and E5103; combined  $N = 11,094$ ) provides evidence of efficacy of bevacizumab in the post-operative adjuvant setting. One additional trial, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-40, evaluated adjuvant bevacizumab but uniquely in this trial, patients received bevacizumab with neoadjuvant chemotherapy as well as post-operatively. Intriguingly, final results from the NSABP B-40 trial demonstrated a significant OS benefit with neoadjuvant and adjuvant bevacizumab versus neoadjuvant chemotherapy alone, although the improvement in DFS did not reach statistical significance [20]. The benefit from bevacizumab was more pronounced in patients with hormone receptor-positive disease, whereas in other neoadjuvant trials (GeparQuinto, ARTemis, and S0800) [8, 9, 11, 21] and the E5103 adjuvant trial [17],

a greater effect was observed in patients with TNBC. Specifically in TNBC, the Cancer and Leukemia Group B (CALGB) 40603 (Alliance) neoadjuvant trial demonstrated a significantly improved pCR rate with 18 weeks of bevacizumab added to chemotherapy for stage II or III disease, but the effect on DFS or OS is as yet unknown [10]. Taken together, none of these results support the use of bevacizumab in the primary breast cancer setting.

The lack of effect of bevacizumab as adjuvant therapy (in contrast to improved pCR rate with bevacizumab in the neoadjuvant setting or PFS benefit in the metastatic setting) is perhaps not surprising when considering the absence of macroscopic disease in patients receiving adjuvant treatment and recent results in preclinical models mimicking adjuvant therapy [22]. A vascular supply is required for tumor growth beyond a few millimeters [23, 24] and it is unclear what proportion of the subgroup of patients ultimately destined to relapse will have had micrometastatic disease of this size during bevacizumab exposure in the BEATRICE trial (1 year) [25]. Proposed mechanisms by which VEGF blockade could influence disease recurrence in the adjuvant setting include prolonging the dormancy of micrometastatic tumor cell aggregates, preventing 'awakening' of dormant micrometastases by blocking new vessel formation, and inhibiting tumor dissemination [26], but there is currently no evidence to suggest that these postulated mechanisms translate into a clinically useful effect of adjuvant bevacizumab therapy for 1 year. A longer duration of adjuvant bevacizumab administration may be hypothesized to improve efficacy [25], especially when considering the transient benefit from bevacizumab seen in the two phase III trials in colon cancer [12, 14]. On the other hand, results from the AVANT trial [12] may be used to argue against indefinite use of VEGF blockade in the adjuvant setting [26].

Recently published preclinical data suggest that the effect of VEGF inhibition on host vasculature depends not only on the class of agent (antibody versus multi-targeted tyrosine kinase inhibition) but also on co-administration with chemotherapy [27]. The researchers concluded that the benefit of an anti-angiogenic therapy can be improved by chemotherapy as well as the efficacy of chemotherapy being increased by combining with anti-angiogenic therapy (i.e. a mutual bidirectional effect). If this holds true in the clinical setting, better outcomes would be achieved by administering all of the bevacizumab in combination with a tolerable chemotherapy in the adjuvant setting, rather than as a single agent for most of the duration. This strategy has been shown to be beneficial in the metastatic setting, where the addition of capecitabine to maintenance bevacizumab in patients with response or stable disease following initial therapy with bevacizumab plus a taxane significantly improved both PFS and OS compared with bevacizumab alone in the randomized phase III IMELDA trial [28]. However, in early breast cancer this approach has been tested only in the ECOG 5103 trial, in which bevacizumab treatment duration was limited to the duration of the standard chemotherapy in one of the treatment arms. There was no evidence that this approach was more effective, but the possibility that a longer duration of concomitant chemotherapy and bevacizumab could be effective remains untested in the adjuvant setting. However, while these may all be interesting hypotheses for exploration, the feasibility, likelihood of success, and priority for conducting further trials of bevacizumab in the adjuvant breast cancer setting are extremely low when considering all available data and emerging research on new strategies, such as the use of capecitabine in patients with residual disease after neoadjuvant therapy [29] or novel agents [30].

Although results of the BEATRICE trial do not help in identifying a targeted treatment option for early TNBC, they provide valuable information that may help in the design of future trials. Firstly, they serve to remind us that treatments demonstrating efficacy in the macrometastatic setting cannot simply be extrapolated to the adjuvant setting, which is biologically very different from the neoadjuvant and metastatic settings. Secondly, results from the BEATRICE trial indicate that the prognosis for patients with early TNBC is better than previously thought. Data from retrospective series suggest that most recurrences occur within 3–5 years of TNBC diagnosis [31]. However, after a median follow-up of 56 months in BEATRICE, the 5-year IDFS rates were 77% in the chemotherapy-alone arm and 80% in the chemotherapy plus bevacizumab arm. These event rates should inform the statistical design of future studies in TNBC. In addition, ongoing gene expression analyses in the pooled dataset from BEATRICE have already yielded fascinating preliminary results in relation to immune signatures [32], which may guide future research in TNBC. Thus, although BEATRICE failed to confirm its primary hypothesis, it has provided the first randomized phase III data on systemic therapy in early TNBC, as well as interesting translational findings, all of which will inform future trial designs in this patient population.

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## figure legends

**Figure 1.** Final OS (intent-to-treat population). BEV, bevacizumab; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; OS, overall survival.

**Figure 2.** Subgroup analyses of final overall survival. BEV, bevacizumab; CI, confidence interval; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HR, hazard ratio; PgR, progesterone receptor.



## **Supplementary figure legends**

**Supplementary Figure S1.** CONSORT flow diagram.

\*Violation of at least one inclusion or exclusion criterion.

**Supplementary Figure S2.** Updated IDFS results (intent-to-treat population, exploratory analysis after a median follow-up of 56 months). BEV, bevacizumab; CI, confidence interval; CT, chemotherapy; HR, hazard ratio; IDFS, invasive disease-free survival.

**Table 1.** Adverse events by treatment phase and study arm (safety population, all patients who received at least one dose of study drug)

| Adverse event                         | From first dose of study drug to 18 months<br>after first dose |   | From 18 months after first dose of study<br>drug to end of study <sup>a</sup> |   |
|---------------------------------------|--|---|---|---|
|                                       | Chemotherapy alone<br>( <i>N</i> = 1271)                       | Chemotherapy +<br>bevacizumab<br>( <i>N</i> = 1288) | Chemotherapy alone<br>( <i>N</i> = 1271)                                      | Chemotherapy +<br>bevacizumab<br>( <i>N</i> = 1288) |
|                                       |  |   |   |   |
| Any adverse event, <i>N</i> (%)       | 1252 (98.5)  | 1274 (98.9)   | 173 (13.6)  | 200 (15.5)  |
| Grade ≥ 3 adverse event, <i>N</i> (%) | 722 (56.8)   | 924 (71.7)  | 58 (4.6)  | 58 (4.5)  |
| Grade 5 adverse event, <i>N</i> (%)   | 3 (0.2)  | 4 (0.3)   | 1 (0.1) <sup>b</sup>  | 1 (0.1) <sup>c</sup>                                |

|  |            |            |          |          |
|--|------------|------------|----------|----------|
| Grade $\geq 3$ adverse event of<br>special interest for bevacizumab,<br><i>N</i> (%) | 499 (39.3) | 687 (53.3) | 9 (0.7)  | 9 (0.7)  |
| Any serious adverse event, <i>N</i> (%)  | 250 (19.7) | 379 (29.4) | 48 (3.8) | 45 (3.5) |

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<sup>a</sup>None of the patients was receiving study therapy during this period; consequently there were no adverse events leading to discontinuation of study therapy.

<sup>b</sup>Hypoxic-ischemic encephalopathy.

<sup>c</sup>Cerebrovascular accident.

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**Supplementary Table S1.** Baseline characteristics and planned adjuvant chemotherapy choice (ITT population)

| Characteristic                        | Chemotherapy alone<br>( <i>N</i> = 1290) | Chemotherapy +<br>bevacizumab<br><br>( <i>N</i> = 1301) |
|---------------------------------------|--|---|
| Age, years, <i>N</i> (%)              |  |   |
| <40                                   | 253 (19.6)                               | 231 (17.8)  |
| 40–64                                 | 916 (71.0)                               | 952 (73.2)  |
| ≥65                                   | 121 (9.4)                                | 118 (9.1)   |
| Menopausal status, <i>N</i> (%)       |  |   |
| Premenopausal                         | 665 (51.6)                               | 676 (52.0)  |
| Postmenopausal                        | 625 (48.4)                               | 625 (48.0)  |
| ECOG performance status, <i>N</i> (%) |  |   |
| 0                                     | 1186 (91.9)                              | 1202 (92.4)   |
| 1                                     | 94 (7.3)                                 | 98 (7.5)  |
| 2                                     | 1 (<0.1)                                 | 0   |
| Missing                               | 9 (0.7)                                  | 1 (<0.1)  |

| Geographic region, <i>N</i> (%)               |            |            |
|---|------------|------------|
| USA, Australia, Western Europe                | 792 (61.4) | 783 (60.2) |
| Eastern Europe, Greece, Israel                | 160 (12.4) | 148 (11.4) |
| South and Central America                     | 37 (2.9)   | 22 (1.7)   |
| Asia, New Zealand                             | 301 (23.3) | 348 (26.7) |
| Race, <i>N</i> (%)                            |            |            |
| White   | 968 (75.0) | 932 (71.6) |
| Asian   | 280 (21.7) | 333 (25.6) |
| Black   | 32 (2.5)   | 29 (2.2)   |
| Other   | 10 (0.8)   | 7 (0.5)    |
| Tumor size, cm (tumor stage),<br><i>N</i> (%) |            |            |
| >0–<2 (T1)                                    | 457 (35.4) | 482 (37.0) |
| 2–<5 (T2)                                     | 759 (58.8) | 755 (58.0) |
| ≥5 (T3)                                       | 71 (5.5)   | 61 (4.7)   |
| Missing                                       | 3 (0.2)    | 3 (0.2)    |

|   |             |             |
|---|-------------|-------------|
| AJCC stage I, <i>N</i> (%)                                | 388 (30.1)  | 382 (29.4)  |
| Hormone receptor status <sup>a</sup> , <i>N</i> (%)       |             |             |
| ER and PgR negative                                       | 1224 (94.9) | 1229 (94.5) |
| ER and/or PgR low   | 66 (5.1)    | 72 (5.5)    |
| Positive axillary nodes <sup>a</sup> , <i>N</i> (%)       |             |             |
| 0   | 814 (63.1)  | 824 (63.3)  |
| 1–3   | 326 (25.3)  | 322 (24.8)  |
| ≥4  | 150 (11.6)  | 155 (11.9)  |
| Ductal/invasive histology, <i>N</i> (%)                   | 1183 (91.7) | 1209 (92.9) |
| Grade 3 tumor, <i>N</i> (%)                               | 895 (69.4)  | 912 (70.1)  |
| Type of surgery <sup>a</sup> , <i>N</i> (%)               |             |             |
| Breast conserving   | 817 (63.3)  | 827 (63.6)  |
| Mastectomy  | 473 (36.7)  | 474 (36.4)  |
| Planned adjuvant chemotherapy <sup>a</sup> , <i>N</i> (%) |             |             |
| Anthracycline   | 468 (36.3)  | 479 (36.8)  |

|                                |            |            |
|--------------------------------|------------|------------|
| Anthracycline and taxane       | 756 (58.6) | 752 (57.8) |
| Taxane                         | 66 (5.1)   | 70 (5.4)   |
| Hormonal therapy, <i>N</i> (%) | 7 (0.5)    | 4 (0.3)    |
| Radiotherapy, <i>N</i> (%)     | 953 (73.9) | 952 (73.2) |

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<sup>a</sup>Stratification factor (data as recorded in interactive voice-response system).

AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ITT, intent to treat; PgR, progesterone receptor.

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**Supplementary Table S2.** Causes of death other than breast cancer recurrence  
(safety population,  $N = 2559$ )

| Cause of death, no. of patients | Chemotherapy alone<br>( $N = 1271$ ) | Chemotherapy +<br>bevacizumab ( $N = 1288$ ) |
|---------------------------------|--------------------------------------|--|
| Total                           | 16                                   | 8  |
| Cardiac failure                 | 1                                    | 0  |
| Coronary artery disease         | 0                                    | 1  |
| Cerebral hemorrhage             | 1                                    | 0  |
| Cerebrovascular accident        | 0                                    | 1  |
| Hypoxic-ischemic encephalopathy | 1                                    | 0  |
| Sepsis                          | 0                                    | 1  |
| Neutropenic sepsis              | 1                                    | 0  |
| Septic shock                    | 1                                    | 0  |
| Shock                           | 1                                    | 0  |
| Varicella zoster pneumonia      | 1                                    | 0  |
| Multi-organ failure             | 0                                    | 1  |



|   |   |   |
|---|---|---|
| Death (not otherwise specified)                         | 1 | 1 |
| Metastasis <sup>a</sup>                                 | 1 | 0 |
| Brain neoplasm  | 1 | 0 |
| Metastatic malignant melanoma                           | 2 | 0 |
| Pancreatic carcinoma                                    | 2 | 0 |
| Acute myeloid leukemia                                  | 0 | 1 |
| Bronchial carcinoma                                     | 0 | 1 |
| Gastric cancer  | 0 | 1 |
| Lung neoplasm malignant                                 | 1 | 0 |
| Pancreatic carcinoma metastatic                         | 1 | 0 |
| <sup>a</sup> Not confirmed as metastatic breast cancer. |   |   |

| <b>Supplementary Table S3.</b> Grade ≥3 adverse events of special interest by treatment arm occurring between 18 months after the first dose of study drug and the end of the study |  |  |
|---|--|--|
| Adverse event of special interest   | Chemotherapy alone<br>( <i>N</i> = 1271) | Chemotherapy + bevacizumab<br>( <i>N</i> = 1288) |
| Any event, <i>N</i> (%)   | 9 (0.7)                                  | 9 (0.7)  |
| Arterial thromboembolic event, <i>N</i> (%)   | 1 (0.1) <sup>a</sup>                     | 5 (0.4) <sup>b</sup>                             |
| Venous thromboembolic event, <i>N</i> (%)   | 3 (0.2) <sup>c</sup>                     | 0  |
| Bleeding, <i>N</i> (%)  | 1 (0.1) <sup>d</sup>                     | 3 (0.2) <sup>e</sup>                             |
| Congestive heart failure, <i>N</i> (%)  | 0  | 1 (0.1) <sup>f</sup>                             |
| Hypertension, <i>N</i> (%)  | 4 (0.3) <sup>g</sup>                     | 0  |
| Proteinuria, <i>N</i> (%)   | 0  | 0  |
| Wound-healing complication, <i>N</i> (%)  | 0  | 2 (0.2) <sup>h</sup>                             |
| RPLS, <i>N</i> (%)  | 0  | 0  |

|   |   |   |
|---|---|---|
| Gastrointestinal perforation,<br><i>N</i> (%) | 0 | 0 |
| Fistula/abscess, <i>N</i> (%)                 | 0 | 0 |
| Febrile neutropenia, <i>N</i> (%)             | 0 | 0 |

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<sup>a</sup>Grade 3 myocardial infarction.

<sup>b</sup>Grade 3 myocardial infarction (*N* = 1), grade 4 myocardial infarction (*N* = 1), grade 4 acute myocardial infarction (*N* = 1), grade 5 cerebrovascular accident (*N* = 1; the same event is also reported within the category 'Bleeding'), grade 3 transient ischemic attack (*N* = 1).

<sup>c</sup>Grade 3 deep vein thrombosis (*N* = 3).

<sup>d</sup>Grade 3 dysfunctional uterine bleeding.

<sup>e</sup>Grade 5 cerebrovascular accident (*N* = 1; the same event is also reported within the category 'Arterial thromboembolic event'), grade 2/3 diverticulitis intestinal hemorrhagic (*N* = 1; repeated grade 2 and one grade 3 episode, attributed to ongoing colonic diverticulitis), grade 4 hematoma (*N* = 1).

<sup>f</sup>Grade 3 cardiac failure congestive.

<sup>g</sup>Grade 3 hypertension (*N* = 4)

<sup>h</sup>Grade 3 wound caused by a traffic accident (*N* = 1), grade 3 wound abscess (*N* = 1).

In each patient, the adverse event occurred before any reported IDFS event, or in the case of the grade 5 cerebrovascular event, was itself the IDFS event.

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IDFS, invasive disease-free survival; RPLS, **reversible posterior**  
**leukoencephalopathy syndrome.**

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**Supplementary Table S4.** Summary of results

| Supplementary Table S4. Summary of results |  |                    |                                     |                    |
|--|--|--------------------|-------------------------------------|--------------------|
| End point                                  | Primary analysis (cutoff: February 29, 2012) |                    | OS analysis (cutoff: June 30, 2014) |                    |
|  | [15]   |                    |                                     |                    |
|  | Chemotherapy alone                           | Chemotherapy +     | Chemotherapy alone                  | Chemotherapy +     |
|  |  | bevacizumab        |                                     | bevacizumab        |
|  | ( <i>N</i> = 1290)                           | ( <i>N</i> = 1301) | ( <i>N</i> = 1290)                  | ( <i>N</i> = 1301) |
| Median duration of follow-up, months       | 31.5   | 32.0               | 56.0                                | 56.0               |
| <b>IDFS</b>                                | <b>Primary</b>                               |                    | <b>Exploratory</b>                  |                    |
| Events, <i>N</i> (%)                       | 205 (15.9)                                   | 188 (14.5)         | 270 (20.9)                          | 244 (18.8)         |
| Stratified HR (95% CI)                     | 0.87 (0.72–1.07)                             |                    | 0.87 (0.73–1.03)                    |                    |
| Log-rank <i>P</i> value                    | 0.18   |                    | 0.11                                |                    |

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|                              |                  |                  |                  |                  |
|------------------------------|------------------|------------------|------------------|------------------|
| 3-year IDFS rate, % (95% CI) | 82.7 (80.5–85.0) | 83.7 (81.4–86.0) | 82.8 (80.7–84.9) | 84.6 (82.6–86.6) |
|------------------------------|------------------|------------------|------------------|------------------|

**OS**

**Interim**

**Final**

|                      |           |          |            |            |
|----------------------|-----------|----------|------------|------------|
| Events, <i>N</i> (%) | 107 (8.3) | 93 (7.1) | 149 (11.6) | 144 (11.1) |
|----------------------|-----------|----------|------------|------------|

|                        |                  |  |                  |  |
|------------------------|------------------|--|------------------|--|
| Stratified HR (95% CI) | 0.84 (0.64–1.12) |  | 0.93 (0.74–1.17) |  |
|------------------------|------------------|--|------------------|--|

|                         |      |  |      |  |
|-------------------------|------|--|------|--|
| Log-rank <i>P</i> value | 0.23 |  | 0.52 |  |
|-------------------------|------|--|------|--|

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CI, confidence interval; HR, hazard ratio; IDFS, invasive disease-free survival; OS, overall survival.

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